CASE REPORT

Adrenal tumours: how to establish malignancy

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SUMMARY

Adrenal masses are commonly found in the course of abdominal investigations and present diagnostic challenges. The foremost issue is whether the mass is the cause of the symptoms being investigated. Additional important clinical questions are: (1) is the adrenal mass benign or malignant and (2) whether the adrenal mass is functional or non-functional? We present a case of a 48-year-old man with severe abdominal pain. Imaging revealed a very large adrenal mass. Differential diagnostic procedures were performed and a diagnosis of primary adrenal lymphoma, an extremely rare cause of adrenal malignancy, was made. He proceeded to chemotherapy with cyclical cyclophosphamide, doxorubicin, etoposide and prednisolone, in addition to rituximab. This case illustrates the importance of establishing the nature of adrenal masses, to rapidly facilitate appropriate treatment.

BACKGROUND

The frequency of adrenal masses increases from 0.2% in youth to 7% in older people.[1] Once discovered, the nature of the mass requires clarification, to exclude hormonal secretion and malignancy. The majority of these lesions are asymptomatic and benign; however, it is essential to recognise adrenal malignancies in order to expedite appropriate therapy. Primary adrenal malignancies in order of decreasing frequency are adrenocortical carcinoma, malignant phaeochromocytoma and, very rarely, primary adrenal lymphoma. Secondary malignancies are more common in the adrenal glands due to the high vascularity of the adrenals.[2] Tumours that commonly metastasise to the adrenals include carcinomas of the lung, breast, kidney, pancreas and melanoma.[3]

CASE PRESENTATION

Case 1

A 48-year-old previously fit and active man presented with severe abdominal and right-sided loin pain, which radiated to the right groin and right shoulder tip. He reported nausea and vomiting, suggestive of intestinal obstruction. Abdominal CT showed an 11 cm adrenal mass. He was referred to endocrine services in a teaching hospital for further assessment and management.

Other important symptoms included hot flushes and night sweats for 2 months. He had occasional headaches, but not of a pounding nature. He also reported shortness of breath of at least 4 weeks duration. He denied symptoms suggestive of vasoconstriction.

There was no relevant medical history. The patient took no medications. There was no significant family history.

INVESTIGATIONS

CT showed a large solid mass in the right adrenal gland abutting the liver and extending across the midline, with a Hounsfield unit measure of 50 (figure 1). Para-aortic lymphadenopathy was evident and there was a large right pleural effusion. The features were suggestive of an adrenal carcinoma.

Fluorodeoxyglucose positron emission tomography confirmed extensive uptake in the large right adrenal mass and in para-aortic lymph nodes above and below the diaphragm. There was also low uptake in the left adrenal gland and in two small nodules in the right lung (figure 2).

Exclusion of phaeochromocytoma was undertaken with measures of plasma metanephrines and 24 h urinary catecholamines, in addition to an iodine^{131}-meta-iodobenzylguanidine scan.

Excision of the mass was the desired next step; however, due to delays in availability of the phaeochromocytoma screen results and the patient's wish for diagnosis, CT-guided biopsy of the right adrenal mass was undertaken. The preferred practice is excision of larger adrenal masses, since biopsy has a risk of seeding tumour along the biopsy track, in addition to retroperitoneal bleeding.

The biopsy revealed a diffuse large B-cell lymphoma of activated B-cell type (figure 3A), with immunohistochemistry positive for CD20, Bcl2, Bcl6, MUM1 and FoxP1. There was evidence of rapid proliferation as indicated by a Ki67 rate of

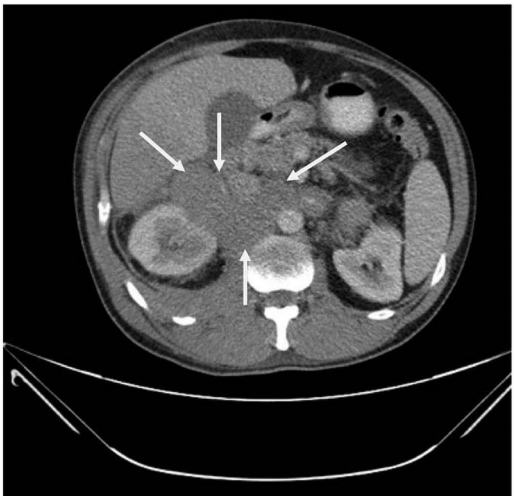

Figure 1 CT of the abdomen demonstrating a 11 cm solid mass arising from the left adrenal gland.

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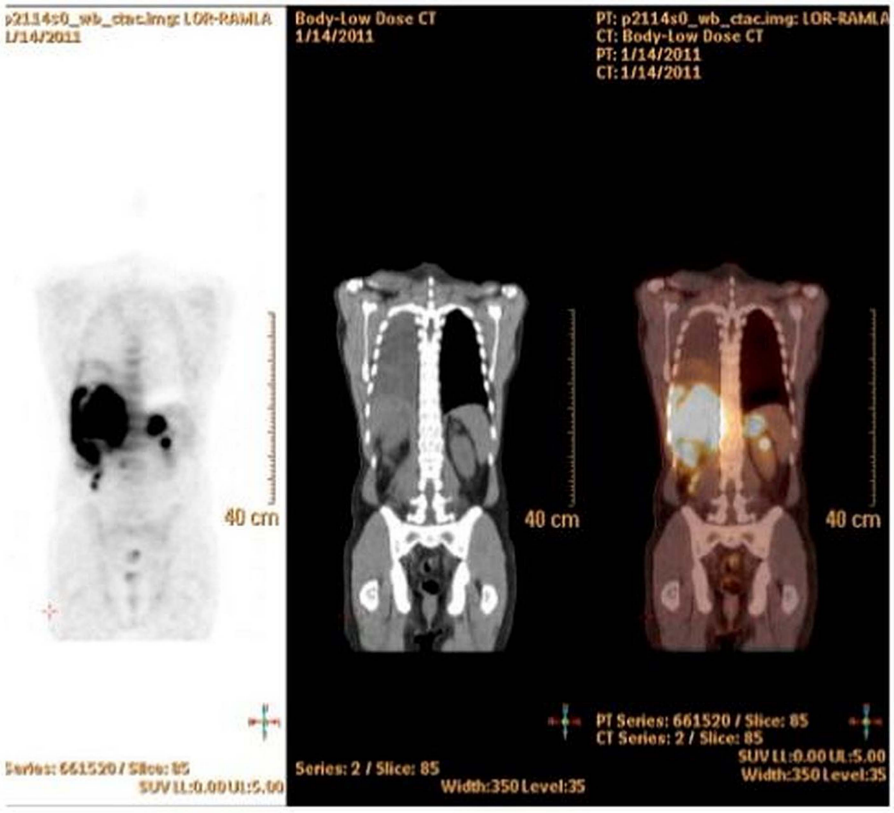

Figure 2 Fluorodeoxyglucose positron emission tomography demonstrating extensive uptake in the large right adrenal mass and in para-aortic lymph nodes above and below the diaphragm.

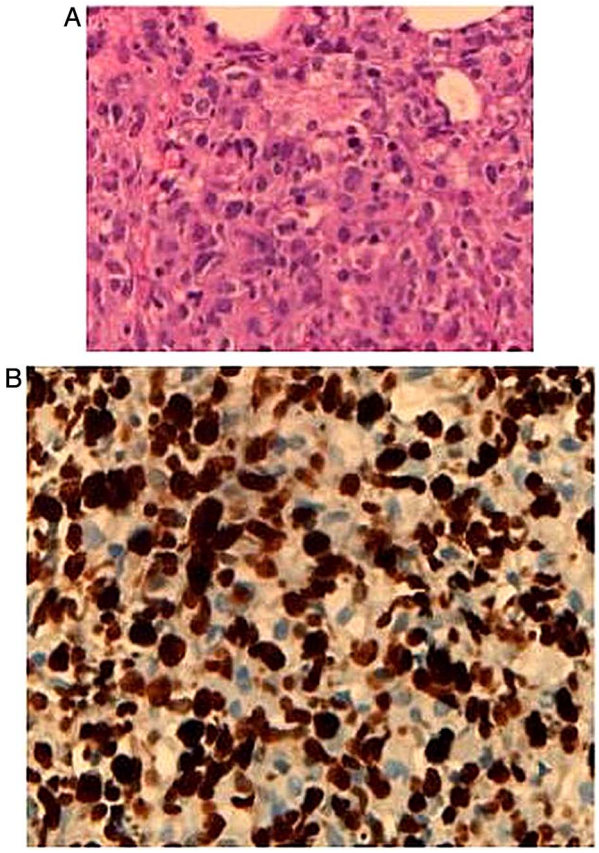

Figure 3 (A) H&E stain showing large atypical lymphoid cells with apoptotic debris and mitotic figures. (B) Ki67 immunoperoxidase stain showing positive nuclear staining in >95% of the lymphoma cells, indicating a high proliferative rate.

>95% (figure 3B). The lymphoma was negative for Epstein-Barr virus (EBV) mRNA.

Further staging was undertaken. A trephine bone marrow biopsy did not show any evidence of bone marrow involvement. The serum lactate dehydrogenase (LDH) level was elevated at 1890 U/L (normal range 0–430 U/L). Aspiration of the pleural effusion drainage showed no malignant cells in the aspirate.

Adrenocortical function was preserved as evidenced by a random cortisol level of 343 nmol/L (200–700).

DIFFERENTIAL DIAGNOSIS

Primary adrenal lymphomas are typically metabolically hyperactive, hypovascular tumours that present on CT scan with slight-to-moderate enhancement. Positron emission tomography (PET) scans can also be useful to differentiate between primary adrenal lymphoma and secondary adrenal lymphoma.[4] While imaging is helpful, definitive diagnosis can only be established based on tissue biopsy. Phaeochromocytoma must be clinically excluded by assessing catecholamine excess states before biopsy is undertaken due to risk of hypertensive crisis.

TREATMENT

The patient started a course of prednisolone then proceeded to a combination lymphoma regimen of rituximab, with a modified CHOP regimen consisting of cyclophosphamide, etoposide, doxorubicin and prednisolone. Etoposide was substituted for vincristine, in view of concerns and risk of possible bowel obstruction.

OUTCOME AND FOLLOW-UP

Six cycles of chemotherapy were completed. Subsequent abdominal CT showed almost complete resolution of the adrenal mass with resolution of the para-aortic lymphadenopathy. The pleural

effusion resolved. Remission was confirmed by PET, with no evidence of fluorodeoxyglucose uptake.

DISCUSSION

Neoplastic involvement of the adrenal gland may result from tumours of the adrenal cortex or adrenal medulla. Primary malignant tumours are rare and include adrenocortical carcinoma, malignant phaeochromocytoma and primary adrenal lymphoma. More frequently, the adrenal glands are involved by metastatic malignancy, particularly from primary carcinomas of the lung, breast, kidney, bladder, pancreas and melanoma.[5] The larger an adrenal mass, the greater the likelihood of malignancy.

Physical examination requires assessment for signs of corticosteroid, catecholamine, aldosterone or androgen excess, in addition to signs of malignancy. Where metastatic malignancy is not suspected, the tumour requires hormone evaluation, with measurement of electrolytes and serum aldosterone-renin ratio (primary hyperaldosteronism), either a 1 mg dexamethasone test or 24 h urinary-free cortisol for Cushing's syndrome, reviewed elsewhere,[6] and androgen levels (virilising primary adrenal tumours). In all circumstances, it is imperative to actively exclude phaeochromocytoma prior to invasive investigations, since biopsy or anaesthesia without appropriate α-adrenergic and β-adrenergic blockade may precipitate a potentially catastrophic, life-threatening crisis. The presence of a phaeochromocytoma is determined by measurement of plasma metanephrines and/or 24 h urinary measures of metanephrine, normetanephrine, epinephrine and norepinephrine.

Hormonal evaluation provides only limited assistance in predicting malignancy. The probability of malignancy is related to tumour size with a high risk of malignancy in masses greater than 6 cm. One series has reported that the risk of malignancy may be as high as one in three for masses greater than 6 cm in size.[7] CT scan using specialised adrenal protocols have been shown to characterise adrenal masses as benign or indeterminate (likely malignant), with a high degree of accuracy.[8] Additional features on CT suggestive of malignancy include an irregular border, a lack of tissue homogeneity, an attenuation value greater than 20 Hounsfield units and a 15 min contrast medium 'washout' less than 40%.[9]

Most patients with malignant adrenocortical tumours are systemically unwell at diagnosis, either because of endocrine disturbances or non-hormonal symptoms including pain, weight loss, weakness and fever.[8] However, a growing number of asymptomatic patients are identified apparently earlier in the course of disease due to incidental pick-up on imaging performed for other reasons.[8] Bilateral enlargement of adrenal glands should raise the suspicion of bilateral phaeochromocytoma, metastatic disease and lymphoma. Ten per cent of adrenocortical carcinomas demonstrate bilateral involvement.[2]

Primary adrenal carcinoma is a rare and highly malignant tumour with a poor prognosis. The incidence is estimated at 2–10 cases per million per year.[8] Diagnosis and accurate treatment can be delayed due to the absence of specific clinical symptoms. Thus, the prognosis is generally poor with a 5-year survival of approximately 35%.[8]

The incidence of malignant phaeochromocytoma is slightly less frequent to that of primary adrenal carcinoma.[8] Clinical symptoms do not help distinguish between malignant and benign phaeochromocytomas and include paroxysmal tachycardia, hypertension, presyncope and/or flushing. Patients with malignant disease tend to have larger tumours and higher urinary metanephrines.[8] The most frequent sites of metastatic deposits are the skeleton, liver, lymph nodes, central nervous system and kidney. The prognosis is somewhat better than adrenal carcinoma, with a 10-year survival of approximately 40%.[8]

Our patient had primary adrenal lymphoma, an extremely rare entity with less than 200 cases reported in the English literature.[4] Adrenal involvement in non-Hodgkin's lymphoma is not uncommon, with up to 25% patients showing involvement of the adrenal gland at some point in their illness. Up to half of the small number of reported patients with primary adrenal lymphoma had adrenal insufficiency and there is a high rate of bilateral adrenal involvement,[10] as suggested in our case by uptake in the contralateral adrenal gland on the initial PET scan. Histologically, the most common type of primary adrenal lymphomas is diffuse large B-cell lymphoma,[11] as with this case.

The presenting symptoms of primary adrenal lymphoma, as with our case, include abdominal or back pain and fever of unknown origin in addition to anorexia, weight loss and signs of adrenal insufficiency.[5]

The pathogenesis of primary adrenal lymphoma is unclear. EBV genome sequences have been detected in some tumour cells, suggesting this virus has a contributory role in malignancy transformation.[10] As human adrenal glands do not contain lymphoid tissue, it has also been suggested that primary adrenal lymphoma may arise from previous autoimmune adrenalitis, which might explain the bilateral involvement.[12]

Treatment with chemotherapy with a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) alone or in combination with rituximab can lead to complete or partial remission, though the overall prognosis is reported to be poor with an average survival of 13 months.[13] The survival time appears to be dependent on the ability to establish diagnosis early. Therefore, a serum LDH level should be included in the diagnostic workup of large adrenal tumours, as it is a common finding in aggressive lymphoma and uncommon in other cases of adrenal tumours unless there is tissue necrosis.

Learning points

- Large adrenal masses are likely to be malignant.
- Prompt investigation to evaluate for or exclude phaeochromocytoma should be undertaken before invasive interventions or surgical resection.
- While metastatic disease is likely if there is bilateral adrenal gland involvement, primary adrenal cancers (adrenal carcinoma, phaeochromocytoma and primary adrenal lymphoma) should also be considered in the differential diagnosis.
- A lactate dehydrogenase level can be helpful to establish the diagnosis of adrenal lymphoma.
- Primary adrenal lymphoma is a rare entity, is often bilateral and can present with symptoms of fevers, night sweats and adrenal insufficiency.

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Competing interests None.

Patient consent Obtained.

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